REMARKS

Claims 22-29 are pending in the present application. Claims 30-39 have been added. Therefore, claims 22-39 will be pending upon entry of the present amendment.

Suport for new claims 30-39 can be found, for example, in the specification as originally filed on page 4, lines 2-9 and 24. No new matter has been added.

Rejection of Claims 22-29 under 35 U.S.C. § 103(a)

Claims 22-29 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ericinska *et al., Journal of Cerebral Blood Flow and Metabolism*, 9:2-19 (1989); in view of Beal *et al., Journal of Neurochemistry* 57(3):1068-1073 (1991), in view of Roberts *et al., American Journal of Physiology* 243(6):H911-H916 (1982) and Nuti *et al. Riv. Neur.* 61(6):225-7 (1991). Applicants respectfully traverse this rejection.

Claims 22-29 are directed to methods for treating a subject with Huntington's disease, by administering to the subject an effective amount of creatine, creatine phosphate or a salt thereof sufficient to reduce or ameliorate Huntington's disease, and further by coadministering to the subject a neurotransmitter, a neurotransmitter analog, an immunomodulating agent, immune suppressive agent, or a steroid.

The primary reference, Ericinska *et al.*, is a general reference which states that the creatine phosphate/creatine system ("PCr/Cr") system is a high energy reservoir present in the central nervous system. Ericinska *et al.* notes that the PCr/Cr system is linked to the adenine nucleotides through a rapid equilibration in the creatine phosphokinase reaction.

Applicants note that the primary reference neither teaches nor suggests methods for treating Huntington's disease, let alone a method for treating Huntington's disease using a creatine compound.

Beal *et al.*, a secondary reference, is about the discovery that aminooxyacetic acid (AOAA) causes excitotoxic lesions, which are similar to those found in Huntington's disease patients. Beal *et al.* states that the excitotoxic legions may be the result of an impairment of the intracellular energy mechanism. In particular, Beal *et al.* notes that "AOAA is a potent inhibitor of aspartate transaminase, which is an essential component of the maleate-aspartate shunt across mitochondrial membranes...Inhibition of aspartate aminotransferase in both brain slices and synaptosomes results in decreased oxygen consumption, decreased glucose and pyruvate oxidation, a decrease in ATP/ADP ratios, and an increase of the NADH/NAD ratio in the cytosol. Interstitial injections of AOAA resulted in fourfold significant increase in stritial lactate levels and significant decreases in ATP concentrations."

Beal *et al.* fails to overcome the deficiencies of the primary reference. Although the Examiner relies on Beal *et al.* to establish that connection between ATP levels and Huntington's disease, Beal *et al.* does not teach that modulation of ATP levels would reverse the effects of treatment with AOAA and/or Huntington's disease. Rather, Beal *et al.* shows that there are many downstream effects of blocking the aspartate transaminase enzyme, including elevated lactate levels and a decrease in ATP concentrations. Beal *et al.* fails to suggest that the legions could be treated by solely increasing the ATP concentrations without additional treatments to decrease the levels of lactate in the cells. Beal *et al.* fails to overcome the deficiencies of the primary reference and fails to teach or suggest that Huntington's disease is caused by a deficiency of ATP. Rather, Beal *et al.* teaches that excitotoxic legions can be formed by treatment of tissue with AOAA.

Roberts *et al.*, a secondary reference, is directed to treating rats with ischemia a creatine analogue. Roberts *et al.* notes that while cyclocreatine significantly increased the time to half-maximal rigor, creatine and other analogs actually ***decreased*** the time to half maximal-rigor as compared to the rats fed the control chow. Therefore, Roberts *et al.* does not provide "motivation to treat disorders via the administration of creatine and/or creatine phosphate because of successful treatment illustrated by Roberts." Applicants disagree because Roberts *et al.* actually show that administering creatine ***shortened*** the time to half-maximal rigor and Roberts *et al.* states that "feeding of creatine or other creatine analogs did not delay rigor."

Roberts *et al.* fails to overcome the deficiencies of Ericinska *et al.* and Beal *et al.*, alone or in combination. Rather, an ordinarily skilled artisan would not be able to use Roberts *et al.* to establish that the administration of creatine compounds would raise intracellular ATP levels, since the experiments on rats gave poor results and certainly did not show successful treatment using creatine, as suggested by the Examiner.

Nuti *et al.* also fails to overcome the deficiencies of Ericinska *et al.*, Beal *et al.*, and Roberts *et al.* Although Nuti *et al.* describes the use of dexamethasone as a potential Huntington's chorea therapy, it does not teach or suggest methods of treating Huntington's disease using creatine in combination with a neurotransmitter, a neurotransmitter analog, a steroid, an immunomodulating agent, or an immune suppressive agent, as claimed by Applicants.

In addition, Applicants submit that creatine has been shown to work surprisingly well in the treatment of Huntington's disease. As described in the declaration of Belinda Tsao Nivaggioli, Ph.D., creatine has been shown to delay progression of Huntington's disease in subjects.

Declaration

The attached declaration of Dr. Nivaggioli presented data which shows that creatine works surprisingly well in the treatment of Huntington's disease.

Creatine has been shown to slow the progression of Huntington's disease when 10 g of creatine were administered to subjects daily for a period of twenty four months. As described below, an open-label pilot study in gene positive preclinical and affected patients with Huntington's disease was done to assess the tolerability, safety, and efficacy of high-dose creatine supplementation. Serial ^{31}P MR spectroscopy (MRS) of muscle was used to assess defects and monitor changes in energy metabolism. ^{1}H-MRS was used to assess brain creatine concentrations.

Thirteen genetically confirmed patients with Huntington's disease were recruited. Three were clinically unaffected and 10 were affected (clinical stages 1 to 3). Four age-matched normal spouse controls were recruited. Exclusion criteria were any intercurrent medical condition or drug or alcohol abuse. The subjects took 10 g per day of creatine and were advised to avoid caffeine and dehydration. Biochemical and hematologic tests were performed at baseline and 3 monthly intervals. Patients were assessed clinically using the United Huntington's Disease Rating Scale [UHDRS] and by MR spectroscopy [MRS] at baseline and 6 and 12 months.

All subjects and controls tolerated creatine treatment, apart from mild nausea and diarrhea. In two subjects, the daily dose was reduced to 5 g after 6 months owing to diarrhea, which settled. One subject discontinued treatment at 6 months and two more discontinued treatment after 12 months owing to poor compliance. Another subject was removed from the study after 12 months because of a rise in serum creatinine (231 mmol/L; normal range 60 to 120).

TMS, functional capacity, and neuropsychology testing showed no significant difference at 12 months. There was no deterioration, and these data indicate stabilization of Huntington's disease symptoms and a delay in the progression of the disease.

After 24 months of creatine treatment, there was no significant change in the mean TMS, functional capacity scores, or neuropyschological testing. MRS studies demonstrated that creatine was elevated in vivo in both brain and in muscle as assessed by N-acetyl aspartate (NAA)/ creatine and phosphocreatine (PCr)/ATP ratios. Mean body weight was slightly increased (72.1 ± 15.6 kg) as compared with baseline (71.0 ± 12.8 kg).

This study showed that 10 g per day of creatine for 24 months is safe and well tolerated. Brain proton spectroscopy demonstrated that creatine crosses the blood–brain barrier and results in increased cerebral concentrations. Muscle MRS, however,

demonstrated only a transient increase in PCr:ATP or PCr:inorganic phosphate ratios at 6 months, but no change at 12 and 24 months.

TMS, functional capacity and neuropsychological testing using the UHDRS showed no significant difference at 2 years from baseline, although the trend was a decline in function, as expected with a cohort of subjects with Huntington's disease. There were differences between the subjects at similar clinical stages, with some showing improvement in the scores, suggesting creatine may be able to slow the progression or even treat Huntington's disease.

The affects of administering creatine to Huntington's disease subjects was also studies in a two-phase open-label dose esclation study. A dose-escalation study (10-40 grams per day) was conducted to determine the maximally tolerated dose (MTD) followed by a de-escalation phase to assess whether brain and serum levels of creatine might be maximal at doses lower than the MTD. Ten subjects were enrolled and followed prospectively for two weeks at each done level increasing in 5-gram increments during dose escalation that lasted 13 weeks. Assessments at each visit included UHDRS, EKG, vital signs, clinical safety and research labs. MRI spectroscopy was conducted prior to baseline at peak done (40 grams) and one month after de-escalation to either 30 or 15 grams daily. To determine an optimal dose, pharmacokinetic as well as clinical data were considered. Once the maximal dose was reached, subjects were assigned one of two lower doses previously taking (15 grams a day (n = 5) or 30 grams a day (n = 5)). Serum creatine was assessed at baseline, at the end of each 2-week dose escalation step and at the end of the de-escalation phase to assess the correspondence between serum and brain levels of creatine at steady state.

All subjects tolerated up to 40 grams/day of creatine during the does escalation and there were no withdrawals. However, there were increased numbers of adverse events at 35 and 40 grams daily, chiefly low-grade nausea and diarrhea. There were no serious adverse events, no significant laboratory abnormalities and no EKG alterations at any of the doses. Although individual subject's creatinine and BUN levels remained within normal clinical ranges, there were changes in average levels. Average creatinine levels increased in a dose-dependent manner from baseline (1.0 ± 0.2 mg/dl) to 30 grams a day (1.28 ± 0.16 mg/dl). Creatinine levels remained stable up to 40 grams/day but decreased in the de-escalation phase. BUN levels did not increase with higher doses during dose escalation and actually decreased somewhat at 15, 25, 30 and 40 grams daily creatine doses perhaps because of an emphasis placed on good hydration. Serum creatine levels increased with each dosage step until they reached a plateau at 30-35 grams/day and actually declined at 40 grams daily.

Changes in UHDRS subscores were not significant. Some subjects felt worse, however, on 35 and 40 grams daily, which could have been due to GI side effects. Brain levels of creatine in the frontal cortex, as assessed by MRI spectroscopy indicated continued increases in brain creatine throughout the dosage range indicating that these high doses are not saturating brain levels. There was a dose dependent suppression of 8OH2'dG to levels greater than seen when subjects were administered 8 grams of creatine per day. Higher doses were associated with further suppression and doses greater than about 25 grams daily were associated with maximum suppression of serum 8OH2'dG levels similar to normal controls. These data suggested that doses higher than 10 grams daily are safe, tolerable and have greater peripheral and brain bioavailability, and are associated with further suppression of a disease related mechanism (oxidative stress as measured by 8OH2'dG). Based on all of this data, 30 grams daily provided excellent tolerability, high bioavailability and maximal biomarker suppression.

Subjects at the end of this study were given the option to continue a long-term study to evaluate the long-term safety and tolerability of high dosage of creatine. Subjects have been followed for nine months on creatine. There have been no significant clinical changes (UHDRS subscores) up to 9 months and there have been no serious adverse effects. Adverse events have been infrequent and mild to moderate in grade and 30 grams daily creatine has been well-tolerated for 9 months. Laboratory abnormalities have been mild. One subject had a Grade 2 (moderate) SGPT level after one-month on 30 grams/day, but his normalized by month 3 without dose adjustment.

Morphometric neuroimaging was performed in all subjects. Longitudinal data from up to three years prior to initiating creatine was available on 6 or the 10 subjects. The rate of thinning of cortical regions in Huntington's disease was modeled based on the longitudinal data and a change in rate was determined for each region of the group while on creatine. Creatine reduced the rate of thinning in almost every region, and the rate of change was determined for each region for the group while on creatine. Creatine reduced the rate of thinning in almost every region, and the rate of change was statistically significant for several regions and amounted to about a 30% slowing.

For at least the above reasons, creatine has surprising and unexpected therapeutic activity for the treatment of Huntington's disease. This surprising activity is not taught or suggested by the prior art. Therefore, Applicants respectfully request that this rejection of claims 22-29 under 35 U.S.C. § 103(a), be withdrawn.

SUMMARY

Amendments to and/or cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's objections and/or rejections. The amendments to and/or cancellation of the claims are being made solely to expedite prosecution of the above-identified application. Applicants reserve the option to further prosecute the same or similar claims in the present or another patent application. The amendments made to the claims are not related to any issues of patentability.

In view of the remarks set forth above, it is respectfully submitted that this application is in condition for allowance. If there are any remaining issues or the Examiner believes that a telephone conversation with Applicants' Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

Date: March 19, 2008

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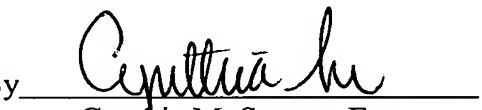
By 

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